Costs of Antiviral Therapy of Chronic Hepatitis B

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Antiviral Treatments

Currently, FDA-approved antiviral drugs in the United States for hepatitis B can be divided into immunomodulatory or stimulatory agents, such as interferon or peginterferon, and nucleoside or nucleotide analogues, such as lamivudine, adefovir, tenofovir, emtricitabine, and entecavir. From an economic perspective, the advantages of the interferon-based therapies include a limited duration of therapy (usually 24 weeks for interferon or 12 months for peginterferon). Administration, however, requires subcutaneous injections, and treatment can be difficult to tolerate because of side effects from the interferon. On the other hand, nucleoside and nucleotide analogues have the advantage of being easily administered as daily oral agents and are generally well tolerated, but treatment may extend for 5 to 10 years or for life. Insufficient clinical evidence exists to support combination therapies, although experience from antiviral treatment of HIV disease suggests that combination therapy should reduce viral resistance and improve health outcomes.

Drug Costs

Monthly U.S. average 2005 wholesale prices for hepatitis B treatments from lowest to highest were $204 for lamivudine 100 mg once daily; $318 for emtricitabine, 200 mg once daily; $478 for tenofovir, 300 mg once daily; $546 for adefovir, 10 mg once daily; $715 for entecavir, 0.5 mg once daily; $1,429 for entecavir, 1.0 mg once daily for lamivudine refractory infections; and $1,540 for peginterferon alfa-2a 180 mcg per week. Similarly, excluding discontinuations and dose reductions and considering only drug costs, annual antiviral drug-only costs from lowest to highest were $2,482 for lamivudine, $3,872 for emtricitabine, $5,811 for tenofovir, $6,647 for adefovir, $8,694 for entecavir in nucleoside-naïve patients, $17,389 for entecavir in lamivudine-refractory patients, and $18,480 for 48 weeks of peginterferon alfa-2a. Although peginterferon alfa-2a has the highest monthly and annual cost, it would likely be given for at most 1 year, whereas the oral agents would likely be given continuously for perhaps a lifetime; so for comparison, the number of years of oral therapy required to equal the cost of peginterferon therapy was 7.4 years for lamivudine, 4.8 years for emtricitabine, 3.2 years for tenofovir, 2.8 years for adefovir, 2.1 years for entecavir in nucleoside-naïve patients, and 1.1 years for entecavir in lamivudine-refractory patients.

Disease Costs

Aside from antiviral drug costs, chronic hepatitis B disease-management costs correlate directly with histological stage. Chronic hepatitis B in the absence of cirrhosis has the lowest annual medical care costs, typically well below that of antiviral therapy. Patients with compensated cirrhosis have higher costs that sometimes reach the cost of a year of antiviral therapy, but usually not. However, once decompensation or hepatocellular carcinoma occurs, annual care costs exceed even the most expensive antiviral drug-treatment annual costs, especially for those who undergo liver transplantation. In this context, for those with chronic hepatitis B without cirrhosis, antiviral drug treatment could be considered as a preventative health measure to decrease the likelihood of developing decompensated cirrhosis or hepatocellular carcinoma in the future.

Cost-Effectiveness

The methodology for the economic assessment of new medical innovations has become standardized, with cost-utility analyses being the most widely recognized and adopted approach

to cost-effectiveness analysis. These analyses incorporate mortality, morbidity from disease and from treatment, and costs. Quality-of-life adjustments account for disability, discomfort, and drug toxicity. Discounting reflects time preferences for the expenditure of money. More specifically, monies spent now are more valuable than monies spent in the future. Thus, applying the standard 3% annual discount rate, $55 spent now for antiviral drug treatment is equal to spending $100 in 20 years to treat future hepatitis B complications. A variety of economic analyses have been published for antiviral treatment for hepatitis B involving no antiviral treatment, interferon only, lamivudine, adefovir, lamivudine with crossover to adefovir if resistant or refractory. In general, they have consistently found antiviral treatment to be "cost-effective" when compared to other common medical interventions.

Typical economic analyses consider single-drug therapies based on clinical trials in treatment-naïve patients, yet in practice, patients undergo sequential therapies. The natural history of patients with resistance who continue the same therapy or who switch therapy is only just beginning to emerge. Such data will assist with the assessment of the cost-effectiveness of drug sequences and the clinical and economic impact of resistance and its treatment. Sequential single-drug therapies likely promote the development of viral resistance. Based on the lessons from antiviral therapy for HIV infection, combination therapy would seem to be most likely to reduce the development of resistance and lead to improved health outcomes, yet clinical trials with combination therapy have not yet borne out this clinical belief. Lastly, recent knowledge about differences in natural history by hepatitis B genotypes has not yet been incorporated into economic models, nor have antiviral responses for different genotypes been uniformly available.

Conclusions

Chronic hepatitis B leads to substantial morbidity and mortality, and the economic costs of the disease are also considerable. Published cost-effectiveness analyses for interferon, lamivudine, and adefovir have consistently found antiviral treatment to be cost-saving or at least cost-effective when compared with other well-accepted medical interventions. Additional economic analyses should be performed with other antiviral treatments; and because comparisons of the alternative therapies in cost-effectiveness analyses require determining the relative benefits of each therapy, these analyses ideally should be based on the results of head-to-head trials. Any other comparison could be confounded by differences in the clinical populations as opposed to drug efficacy. In addition, standardizing reporting requirements for descriptions of the patient populations and for outcome measures would facilitate clinical and economic comparisons. Finally, to help policymakers, health care payers, and physicians determine the value of treatments for hepatitis B, cost-effectiveness analyses will complement clinical studies by translating health outcomes into standard health economic outcome metrics to determine whether hepatitis B therapies provide sufficient clinical benefit to justify their cost.